Protocol Application Reviewed by Children's Hospital and Regional Medical Center IRB

A. Background or rationale for this activity. Cite previous work in the area by you and others with an emphasis on the problems or deficiencies in the existing data base. Include specific bibliographic references for all work cited.

Type 2 diabetes (the most common form of diabetes) used to be found almost exclusively in adults. However, in the past 10 years, the incidence of type 2 diabetes among children has increased dramatically (about 10 fold). This increase seems to be due to a simultaneous increase in childhood obesity. Asians are a rapidly growing minority group in the United States that is poorly represented in epidemiologic research. Asian adults, despite having a low prevalence of obesity, appear to be at increased risk for diabetes due to a predisposition to accumulate fat inside the abdomen. While no data are available on type 2 diabetes among Asian-American children, in Japan type 2 diabetes prevalence among school children has increased markedly in recent years as obesity has become more prevalent. Rates are likely to be even *higher* among Japanese-American children in the United States than children in Japan, since obesity is more prevalent in this country. *Although* the rates of type 2 diabetes have dramatically increased, the absolute number of affected children is still relatively small. Therefore, we feel that this problem is best studied by looking at changes in glucose metabolism that are related to diabetes around the time of puberty, when children appear to be at the greatest risk.

SIGNIFICANCE

The risks of diabetic complications, such as renal failure, lower extremity amputation, blindness, and cardiovascular disease, increase with duration of diabetes. Thus, the increased prevalence of type 2 diabetes in children is especially concerning. Based upon observation from studies among adults, Asian-American children are probably at increased risk for type 2 diabetes, yet they are an under-studied group. Since the risk of childhood type 2 diabetes is maximal around age 13.5, it appears that important physiologic changes occur during puberty that increase the risk of diabetes. The proposed study will provide important information on the metabolic features of the insulin resistance syndrome in Japanese-American children as they progress through puberty, and will also provide an opportunity to better understand the effect of Japanese ancestry on metabolic risk. These studies will probably be relevant to other Asian populations in the United States.

B. What specific question(s) does this project attempt to answer?

The long-term aim of this study is to better understand in children the metabolic changes that precede the development of type 2 diabetes, and the influence of Asian ethnicity on diabetes risk. Prepubertal children of varying proportions of Japanese ancestry (ranging from 0 to 100%) will be followed into and through puberty.

Specific aim 1: To describe in prepubertal (8-10 years), nondiabetic children the metabolic and obesityrelated factors that are associated with the insulin resistance metabolic syndrome. These include fasting plasma lipids (cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol), LDL size, blood clotting factors (plasminogen activator inhibitor-1, fibrinogen, C-reactive protein), glucose, insulin, C-peptide, and proinsulin; glucose tolerance, total body fat,; body fat distribution; and body mass index.

Hypothesis 1: Features of the metabolic syndrome (abnormal response to insulin, high blood pressure, and abnormalities of blood cholesterol and other lipids) are found in some prepubertal children.

Specific aim 2: To assess the ability of cells in the pancreas to make insulin by measuring fasting plasma insulin, C-peptide, proinsulin, and acute insulin response to glucose by an intravenous glucose tolerance test.

Hypothesis 2: Pancreatic islet B-cell dysfunction is evident in some children.

Specific aim 3: To describe the changes in these factors as children progress through and complete puberty. Tanner staging is used and plasma testosterone, estradiol, DHEA-S, IGF, IGFBP-3 are measured to describe pubertal stage.
Hypothesis 3: Puberty is associated with changes in body fat distribution and metabolic parameters in a direction consistent with *higher* risk of glucose intolerance and cardiovascular disease.

Specific aim 4: To describe the relationship of lifestyle factors (diet and physical activity) to the metabolic and adipose factors, and changes therein.
Hypothesis 4: Diet and physical activity are important predictors of body fat and metabolic changes in children.

Specific aim 5: To describe the relationship of proportion of Japanese ancestry to the metabolic and obesityrelated factors, and changes therein.
Hypothesis 5: A higher proportion of Japanese ancestry is associated with a greater predisposition to the metabolic syndrome and diminished insulin secretion.

C. Explain how this project is specifically designed to answer the questions being asked (e.g., caselcontrol comparison; randomized double-blind trial).

This is longitudinal, observational study of prepubertal children.

D. Describe how your data will be recorded, including the outcome variables and the methods for analysis to be used. Submit data collection sheets, if available. NOTE: Statistical consultation is encouraged.

Data will be entered into a data management system on a microcomputer for storage and analysis. The outcome variables of primary interest in this study are B-cell function, body fat distribution and other features of the metabolic syndrome: blood pressure, dyslipidemia, insulin resistance, and hyperinsulinemia. As indicated by the 5 specific aims of this research, 5 hypotheses are being addressed, and data analysis will be used that is appropriate to each hypothesis and aim. In general, we hypothesize that the listed metabolic features are influenced by environmental factors (sedentary lifestyle and high caloric, high fat diet), pubertal development, and ethnicity: Linear regression and analysis of covariance (ANCOVA) will be used to test these hypotheses. The specific statistical methods are described in detail in the grant application. In order to understand the features of the metabolic syndrome in children and adolescents, we plan to measure the change in these variables before puberty (baseline) and at 2-year follow-up, when approximately 42% of children will have entered early to mid-puberty (breast Tanner stage 2-3 or testicular volume ? 4ml.). This will allow the effects of puberty to be distinguished from the effects of aging alone.

Because individuals from the same family may share genetic and environmental factors, analyses that include siblings or cousins may violate statistical assumptions of independence. We anticipate few siblings given the small sibship size in this population and the narrow eligible age range. Cousins share only 12.5% of their alleles on average,
so we do not expect strong intercorrelations. Nevertheless, analyses will utilize a robust variance estimator (or sandwich estimator) with kindred as the clustering variable. This procedure uses a robust estimate of variance and relaxes the assumption of independence for individuals from the same kindred.

E. SUBJECTS:

1. **Approximate number and ages:**

Subject Group	How Many		Age	ange
	Current Year	Entire Study	Current Year	Entire Stud
Normals/Controls		300	8-10 o	8-10 o
Patients		0		
Other (specify, e.g., parents, other family members, school teachers)		150 Caucasian cousins	8-10 yo	8-10 yo

2. Criteria for selection for each subject group.

Eligible Participants

Healthy prepubertal children, aged 8-10, who are either of Japanese ancestry (any proportion) or are Caucasian cousins of mixed Japanese-Caucasian participants will be eligible for this study. Participants must anticipate living in the Seattle area for at least 5 years. A maximum of one boy and one girl per nuclear family will be enrolled (see section D5a).

3. Criteria for exclusion for each subject group.

Children who are non-English speaking, and children who do not have an English speaking parent will be excluded. Children who are on chronic medications will be excluded; however, children with recent antibiotic use for an acute illness may participate. Girls with Tanner breast stage >_ 2 and boys with testicular volume >_ 4 ml at baseline will be excluded. Children who are unable to cooperate with the study protocol (IV placement, lie still for imaging procedures without sedation) will also be excluded.

4. **Source of subjects. Include letters of cooperation, as appropriate, from agencies or other institutions involved in subject recruitment.**

We will use existing contacts in the Japanese American community to recruit children of Japanese descent and Caucasian cousins of mixed Japanese-Caucasian participants. These include our Community Advisory Board members (see http://dept.washington.edu/jacds/).

This is a critically important aspect of this research and we will depend heavily upon the experience we have gained and the extensive networking we have established over the past two decades in performing the Japanese American Community Diabetes Study. We will recruit children of Japanese ancestry through a variety of techniques that have proven to be successful in the past. Letters will be sent to the approximately 600 living adult participants in our Japanese American Community Diabetes Study, residing in King County, Washington, informing them about the expansion of our study to include children and asking them to contact us if they know of eligible children who may be interested (see attached draft of recruitment letter). Our website (http://depts.washington.edu/jacds/) will include recruitment information. We will also carry out community-wide publicity through community events and activities as arranged through our Community Advisory Board (such as writing articles for the Tayori newsletter and participating in church bazaars). We will send information and recruitment letters to Japanese households in King County using a comprehensive mailing list. In addition, we will target private Japanese language schools and other activities in which Japanese-American children are likely to participate. We will

also ask parents whose participant children are of Japanese/Caucasian ancestry for permission to recruit Caucasian cousins.

5. Does subject population Include equitable gender and minority representation?

[ ] Yes [X] No, explain

Gender representation: Male and female subjects will be enrolled on a 50/50 basis.

Minority representation: The study focuses on children of partial to full Japanese descent, and Caucasian cousins of mixed Japanese-Caucasian participants.

Asian Americans are a diverse population. Japanese Americans are the third most populous Asian subgroup in King County, Washington. Unlike other Asian subgroups, the vast majority of Japanese Americans living in this region are U.S. born and their families have resided here for several generations. This distinction is highly relevant to this study. Dietary habits are associated with duration of time in the United States. The rise in diabetes among Japanese children coincides with the adoption of a "westernized" lifestyle. Thus, in order to understand diabetes risk in Asian-American children, it is preferable to study children whose lifestyle is typically American. Findings in children of recent immigrants may vary with time since immigration, and may not be generalized to subsequent generations. Furthermore, follow-up is likely to be enhanced by geographic and economic stability, and English proficiency will facilitate recruitment of participants.

Another important reason to focus on Japanese Americans is their history of participation in similar local studies. We have conducted the Japanese American Community Diabetes Study in adults since 1983, with superb participation and cooperation by the Japanese-American community, and this will provide an excellent basis for recruitment of children for this study.

6. How and by whom will the subjects be approached? Explain what steps you will take to avoid coercion and to protect privacy. (NOTE: In most cases, parents or guardians should be approached before giving information to the minor.) If to be used, submit adverfsements/flyers/contact letters, explaining how and where they will be distributed. For information about recruitment advertisements within CHRMC, call 526-2023.

See above recruitment strategies. Current participants in the Japanese American Community Diabetes Study already receive an update newsletter from us. Parents or guardians of eligible children who are interested in joining the study will contact us privately and directly through phone call, email or written response to an enrollment flyer. In addition, a flyer may be provided to our contacts in Japanese American community organizations for inclusion with their routine mailings. This flyer will be developed with input from our Community Advisory Board. Prospective participants' names are kept confidential among study personnel. (See attached letter of support from Dr. , chair of our Community Advisory Board)

Those children (and their parents or guardian) who are interested in joining the study will contact us privately and directly through phone call, email or written response to an enrollment flyer. Recruiters who are not actual members of our study personnel will not be advised of the names of those they have successfully recruited.

7. Will subjects receive an inducement, e.g., payment, services without charge? If so, what amount or how? What is the reason for this inducement?

Participants will be offered compensation for time and discomfort in the form of gift certificates. Twentyfive dollar gift certificates will be provided for each evaluation. Children will be allowed to select from a wide range of gift certificates, such as movie theaters, video rental, sporting events, activities (such as miniature golf or bowling), and toy stores). Parking vouchers will be provided to parents.

F. PROCEDURES INVOLVED. Provide a short description of the sequence and methods to be used, e.g., administration of drugs, volume of blood, size of biopsy, questionnaire, name of psychological test. Include procedures planned for screening and followup phases. If audiovisual, tape recordings, or photographs will be made, describe their use. Add sheets if necessary.

Evaluations will take place at the University of Washington General Clinical Research Center (GCRC) pediatric satellite facility at Children's Hospital and Regional Medical Center. Information about ethnicity, dietary and physical activity habits, pubertal maturation, and features of the metabolic syndrome will be obtained at baseline. All participants must be prepubertal at baseline. All children will be re-examined at 2 years. At 2 years, about 42% of participants will be pubertal, allowing the effects of early- to mid-puberty to be distinguished from the effects of aging.

Interview

The following information will be obtained from the child's parent. Demographic information will include date and country of birth, years of US residence, non-English language use, parental educational level, and household income. If the child's parents are divorced, the custodial parent(s) will be determined and the household income adjusted accordingly. For example, if a child resides 40% of the time with the father and 60% of the time with the mother, the child's household income will be calculated as 0.4*(father's household income) + 0.6*(mother's household income). A brief medical history will be obtained to confirm that the child has no chronic medical problems and is not acutely ill, as well as questions about medications, body odor/deodorant use, menarche (girls) and voice change (boys). Family history of medical conditions (diabetes, heart disease, hypertension, hyperlipidemia, or stroke) and ethnicity of parents and grandparents will be obtained.

Physical Examination and Anthropometry

Standing height will be measured without shoes to the nearest 0.lcm. Body weight in light clothing, without shoes, will be measured to the nearest 0.01kg. BMI will be calculated (kg/m^2). Two waist circumferences will be measured with a nonelastic tape: at the superior margin of the iliac crest and at the midpoint between the iliac crest and the lowest rib margin in the mid-axillary line. Hip circumference will be measured at the maximum extension of the buttocks. Supine blood pressure will be measured using a mercury column sphygmomanometer and an appropriately sized cuff three times, and the mean of the second and third measurements will be used to estimate systolic and diastolic blood pressure. Heart rate will be counted at the radial pulse for 15 seconds to calculate beats/minute.

An experienced clinician will examine the neck and skin folds for the presence or absence of acanthosis nigricans. Visual inspection of the breasts (female), genitalia (boys), and pubic hair will determine Tanner stage of sexual development. Testicular volume will be measured in boys using a Prader orchiometer. These standard techniques for determining sexual maturation have been shown to be appropriate for Japanese children. Because pubic hair development is significantly slower in Japanese children compared to Caucasians, despite earlier skeletal, genital and breast maturation by approximately one year, primary analyses will not use pubic hair determinations of Tanner stage. Sex hormone levels will be used to validate pubertal status (see section D2f).

Dietary Assessment

Three-day food records and 24 hour dietary recall will be used to measure dietary habits. Because children have difficulty recalling dietary details, a registered dietitian will educate children and parents about estimating portion sizes and techniques for recording dietary intake throughout the day. School lunch menus will be used to improve detailed recording about meals eaten away from home. Participants will be prompted to include snacks. The interviewer will be instructed to convey neutrality about reported food intake, so as not to discourage reporting of "unhealthy" or "forbidden" foods. The data will be summarized as total caloric intake (kcal/day) and percent of kcal from carbohydrate, fat (total and saturated), and protein (total and animal). Because under-reporting of food intake increases with the age of the child, baseline dietary data will be used for longitudinal analyses.

Physical Activity Assessment

Physical activity before, during, and after school, will be estimated using a checklist. The checklist asks about activities during the previous day, and includes time spent watching television, videos or a computer screen. Responses will be weighted for level of intensity based on standard energy intensity estimates. This checklist has been validated as a measure of moderate to vigorous physical activity using heart rate (r = 0.5) and accelerometer (r = 0.3) data. Parental estimates of television viewing have been validated using videotaped observation, and have been shown to have good test-retest reliability among children. Both the child and a parent will be asked to complete these questionnaires, and the data analyzed separately. While physical activity assessment in children is challenging, physical activity estimates based on these questions have been associated with overweight status and improvements in BMI and fitness following an educational intervention. These data will be summarized as: a) minutes of sedentary activity; b) minutes of moderate to vigorous physical activity; and c) metabolic equivalents (METs) of moderate to vigorous physical activity, where 1 MET is equivalent to the resting metabolic rate. Fasting blood levels

Plasma immunoreactive insulin, proinsulin, C-peptide, glucose, hemoglobin Alc (HbAlc), cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, LDL size, hematocrit, testosterone (boys), estradiol (girls), dihydroepiandosterone sulfate (RHEA-S), insulin growth factor (IGF-1), insulin growth factor binding protein (IGFBP-3), plasminogen activator inhibitor-1 (PAI-1), fibrinogen, and C-reactive protein will be measured following a 10-hour overnight fast. A blood sample will be centrifuged on-site at the GCRC .- measure hematocrit and ensure that children are not anemic prior to obtaining further blood samples. White blood cells from all blood samples will be pooled and saved for their DNA. DNA samples will be used in future studies to examine gene markers that are identified as being associated with diabetes and cardiovascular disease. All participants will be given the option of deciding whether to have DNA samples saved without precluding their participation in this study.

Intravenous glucose tolerance test (IVGTT).

Following an overnight 10-hour fast, 25% glucose (0.5g per kg body weight, to a maximum of 35g) will be administered intravenously over 3 minutes. Prior to administration of glucose, baseline blood samples will be drawn at 20 minutes after intravenous cannula placement, and again in 5 minutes (immediately before glucose administration) for measurement of plasma glucose and insulin. Samples for plasma glucose and insulin will be drawn at 0, 1, 2, 3, 4, 5, 7, 10, 15, 20, 30 and 40 minutes following the glucose infusion. This protocol was selected because it is widely used and well tolerated in young children, including in the DPT-1 study. The glucose disappearance constant (Ko, the natural logarithm of the rate of fall in glucose between 10 and 30 minutes) provides an assessment of glucose metabolism dependent upon a combination of insulin sensitivity and secretion.

Insulin sensitivity

Fasting insulin and C-peptide will be used to estimate insulin sensitivity. Fasting insulin and glucose will also be used to calculate insulin resistance according to the homeostasis model assessment (HOMA. HOMA insulin resistance correlates well with insulin resistance determined by euglycemic clamp, and is superior to fasting insulin alone when compared to Bergman's model of insulin sensitivity. HOMA has been used to estimate insulin sensitivity in children of many ethnic backgrounds.

Body composition

Dual-energy x-ray absorptiometry (DXA) will be used to measure total fat mass, lean body mass, and regional fat mass in the abdomen. Radiation exposure is about 10 mrem, or about 3% of the average natural background radiation exposure for an individual living in the United States. DXA is frequently used to measure body composition in children with good reproducibility. Importantly, DXA measurements are not affected by ethnicity, whereas other measures of body fat, such as bioelectrical impedance, require validation of population specific equations. While DXA can provide a regional measure of abdominal fat mass, it does not distinguish between subcutaneous and intra-abdominal fat. DXA measurements will be performed at the University of Washington Medical Center.

Magnetic resonance (MR) imaging will be used to measure subcutaneous and intra-abdominal fat at the level between the fourth and fifth lumbar vertebra (L4-5). While MR is relatively expensive, intra-abdominal fat is an important component of the insulin resistance syndrome (see section B2b). Unlike computed tomography, MR does not generate radiation exposure, which is an important consideration in pediatric subjects. Attempts to estimate intra-abdominal fat from anthropometric

measures have shown unacceptable accuracy in children. A single observer will obtain all measurements throughout the study to improve accuracy. MR will be performed at the University of Washington Medical Center.

Total Volume of Blood to be Drawn: The total volume of blood drawn per year will not exceed 45 cc. This is considerable less than 2.5% of blood volume for an 8 year old child of average weight (25 kg.), estimated to be 55cc.

1. **Explain (a) how study procedures differ from standard care and (b) whether this study will preclude or delay standard care.**

   These are healthy children. All procedures are being performed solely for the purpose of research. Normally, none of these procedures would be done on healthy children.

2. **If any deception (withholding of complete Information) is required for the validity of this activity, explain why this is necessary and attach a debriefing statement.**
   No deception will be used.

3. **Location where procedures will be carried out.**

   University of Washington Medical Center, Seattle, WA

   University of Washington General Clinical Research Clinic Satellite at Children's Hospital & Regional Medical Center, Seattle, WA

4. **What CHRMC resources will be required, e.g., equipment, space, nursing staff, pharmacy, laboratories, medical records? CRC space and personnel Endocrinology study coordinator time.**

5. **How will the CHRMC resources be funded?**

   NIH Grant

6. **Will subjects be charged for any study procedures?** [X] No [ ] Yes, explain.

G. RISKS AND BENEFITS. The IRB will use this information to determine whether the benefits outweigh the risks.

1. **Nature and amount of risk from all study procedures, drugs, devices, interviews, and questionnaires. As applicable, include physical risks (such as side effects from drugs), psychological risks (such as substantial stress, discomfort, or invasion of privacy), and social risks (such as jeopardy to insurability or employability).**

Serious potential risks from this study are extremely unlikely. Risks include discomfort, ecchymoses, or inflammation from venipunctures. An experienced pediatric nurse will place the intravenous catheter (IV) and blood will be drawn through the IV to minimize these risks. Entertainment (such as electronic games, television, and videos) will be available to distract children during venipunctures. There is also risk of pain and inflammation if glucose is injected extravascularly. While examination for sexual maturity is essential to interpretation of the study results, efforts will be made to minimize embarrassment. Children may choose to be examined in the presence of their

parents, and all exams will be performed by an experienced clinician with a chaperone present. Moreover, since assessment of sexual maturation is a standard component of a routine pediatric examination, most children will already be familiar with this procedure. The radiation exposure associated with DXA is less than 0.1 microGy (10 mrem) which is at the lower end of the exposure range for diagnostic radiographs. This represents about 3°% of the average annual exposure from natural background radiation in the United States. Magnetic resonance imaging does not involve radiation exposure. No investigational drugs will be used.

2. Describe the expected benefits for the Individual subjects and/or society.

There will be an educational benefit to all children and their parents regarding lifestyle and health. Children and their parents will have the opportunity to ask physicians, nurses, and registered dietitians questions about nutrition, obesity, physical activity, and diabetes risk. While most children are expected to be healthy, a beneficial effect on the medical care of some children (e.g. those with hyperlipidemia or hypertension) is possible. All participants may derive future benefit from the increased knowledge about type 2 diabetes and associated conditions expected to be gained from this study.

Currently more than 20% of children in the United States are obese, and the numbers are increasing. There is evidence that obesity-related diseases such as diabetes, which until 10 years ago were seen almost exclusively in middle-aged adults, are now affecting children. Complications, such as limb amputation, blindness, and kidney failure are related to duration of disease. Therefore, the younger the age of onset, the greater the chance of serious complications or premature death. Furthermore, there is evidence that Asians are affected disproportionately by the health consequences of excess weight, even at relatively low degrees of overweight. Thus, there is substantial potential benefit to society as a whole to increase our knowledge about weight gain, metabolic changes, and risks of type 2 diabetes in children so that better treatment options can ultimately be developed. We acknowledge that there are significant risks of discomfort to participants in this study, although there is negligible risk of serious harm. We feel that by taking precautions to minimize discomfort, ensuring as pleasant an experience as possible for the participants, and providing children and their parents information about this public health problem, that the benefits to society will clearly be outweighed by the risks.

H. FOLLOW-UP planned at completion of study, e.g., return of information to subjects, referral to appropriate practitioners. Explain what information families will receive at what point in the research, and who will convey the information to families.

Results which may be relevant to the participant's medical care (e.g. height, weight, blood pressure, hematocrit, glucose, cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) will be sent by mail to the child and consenting parent. If the parent provided written consent at the time of the visit, these results will also be provided to the child's physician. All other study information, including genetic information, will be completely confidential and will be used for research purposes only.

1. Are results likely to have diagnostic, predictive, or reproductive implications? [ ] No [X] Yes, explain

It is possible that a small number of children will be found to have elevated blood pressure, blood sugar, or cholesterol. As described above, clinically relevant information will be sent to the child and their parent. These results will be noted as normal or abnormal. If abnormal, we will

provide written instructions to contact their regular physician for further evaluation. If this were to occur, it would likely be beneficial to the child, since these potentially treatable conditions may otherwise have gone undetected.

There is an extremely low likelihood that one of our research-oriented measures could indicate a serious medical condition. For instance the DHEA-S level, which is being used to validate pubertal stage, could be extremely high, suggesting a tumor. Likewise, the MRI, being used to measure intra-abdominal fat, could show an
abnormal mass. In this event, we will contact the child's parent and inform them of the result, and recommend evaluation by the child's regular physician. We will also request permission from the child's parent to notify the child's physician of these findings. If this were to occur, it could actually be of benefit to the child, since the research protocol may have detected a serious condition at an early and curable stage.

2. If applicable, explain how interim or inconclusive results will be handled and whether subjects will be given the opportunity not to receive information about themselves.

There are no interim results. Clinically relevant results will be sent with an interpretation as to whether the results are normal, abnormal, or borderline. In the unlikely event that participants do not wish to receive results, none will be sent. This has not happened with any of our previous participants.

Please see page 10, section J 5(c) regarding stored DNA samples.

I. ADVERSE EFFECTS

1. How and by whom will adverse effects be handled?

[X] By investigators [X] Referred for appropriate care [ ] Other, explain.

2. Are facilities adequate for handling adverse effects? [X] Yes[ ] No, explain

3. Who will be financially responsible for treatment of adverse effects resulting from study procedures? [ ] Study sponsor [ ] Subject [X] UW compensation plan [ ]Other, explain

J. CONFIDENTIALITY

1. Will study datalsamples be anonymous (no possible link to identifiers)? [ ] Yes [X] No

2. Will data/samples be confidential (identifiable with a unique study code) and will the key to the code be kept separate from the data/samples? [X] Yes [ ] No If "No," explain.

3. Will any other agency or non-study personnel have access to identifiable

[ ] Yes [X] No data/samples? If "Yes," specify and explain.

4. What provisions will be made for controlling access to the data/samples?

[X] Computer with restricted access [X] locked file [ ] Other, explain

Data will be coded. A master list linking data to individual subjects will be securely maintained separately from the data in locked filing cabinet and in a password protected computer file. The computer file will be necessary so that we can send out letters to participants reminding them of follow-up; it will contain study id number, patient name and address. Direct identifiers will be removed from paper data collection forms as soon as data collection is complete, and the data has been entered. Computer files of data results will not contain direct identifiers.

This is a longitudinal study which requires that we retain the ability to contact participants for future followup. The initial funding period we are requesting is for 5 years, but we plan to renew the grant for future follow-up. The direct identifier link will destroyed if no additional funding to continue the study has been obtained for 15 consecutive years after the most recent data collection.

5. Does this study involve long-term storage or "banking" of the datalsamples?

[X] Yes [ ] No

If "Yes," explain how the banked data/samples will be handled:

(a) If a subject wishes to withdraw from a study after It has begun or after it has been completed.

Subjects may withdraw at any time by notifying any of the investigators listed on the consent form.

(b) If another investigator wishes to use the banked data/samples for the same research purposes.

Data and samples may be used only if in collaboration with one of the original investigators.

(c) If either you or another investigator wish to use the banked data/samples for different research purposes.

Use of banked data or samples for unrelated research purposes will not be permitted without reconsenting the participants.

Note that we do plan to bank DNA for future analysis. The research purpose will be the same as for this study. Children and parents will be advised at the time of consent that DNA will be saved for analysis in future studies, and all participants will have the option of declining to have DNA samples saved. These future studies will involve looking to see whether specific genes or gene markers related to glucose or fat metabolism, diabetes, or cardiovascular disease are related to other metabolic markers of diabetes risk in our study. Thus these future studies are related to the original research purposes. It is hoped that this information will improve our understanding of the pathophysiology of the insulin resistance syndrome so that better treatments can be developed. It is highly unlikely that this information will be clinically relevant to an individual child, as no diagnostic DNA tests currently exist for type 2 diabetes or cardiovascular disease. Furthermore, the DNA analysis will be performed in a research lab, not a clinical lab. It will not be possible for the lab performing this analysis to directly link the results of the DNA analysis to a specific individual by name, as the samples will be coded by study ID number only. We will explain that use of this information is for research purposes only, and results will not be shared with study subjects, their parents or their physician. We will submit an addendum Human Subjects Application at which time these samples are ready to be analyzed, providing information about the specific tests to be performed, and including details about where the samples will be run. DNA samples will be labeled by

study ID only, and will not be labeled with direct identifiers. DNA will be stored in the laboratory of Dr. Wilfred Fujimoto until ready for processing.

VII. CHECKLIST FOR INVESTIGATORS:

A. Will any group, agency, or organization be involved? [ ] Yes [X] No If yes, explain:

B. RADIATION. Will materials with potential radiation risk be used, e.g. x-rays, radiopharmaceuticals, radiation therapy? [X] Yes [ ] No If "Yes:" DEXA

1. Is this use investigational, experimental, or with greater frequency or Intensity so that it might be considered a departure from the standard care for the patient's condition?

[X] Yes [ ] No [ ] Don't know

If the answer is "Yes" or "Don't know," the project will require review by the Radiation Safety Committee. Submit a copy of the IRS application and a cover letter explaining the use of radioactive materials to David Rosenbaum, MD, Radiology, CH-69.

2. Has project been approved by the Radiation Safety Committee? [ ] Yes [X] Pending

Submitted to UW Radiation Safety Commitee, as testing with radiation to be done at UW.

C. BLOOD DRAWS. The chart below represents average blood volume for the ages specified, premature infants through 2 years.

Age	Total Blood Volume	2 1/2% Volume
26 wk	104 ml	3 ml
30 wk	158 ml	4 ml
34 wk	242 ml	6 ml
Term	340 ml	9 ml
3 mos	500 ml	13 ml
6 mos	670 ml	17 ml
9 mos	800 ml	20 ml
12 mos	900 ml	23 ml
24 mos	1100 ml	28 ml

1. Will blood be withdrawn for research purposes in an amount greater than 2 1/2% for a single draw or 5%. within a two-month period? If "Yes," explain why this is necessary and comment on associated risks. [ ] Yes [X] No

The total volume of blood drawn per year will not exceed 45 cc. This is considerable less than 2.5% of blood volume for an 8 year old child of average weight (25 kg.), estimated to be 55 cc.

2. Are combined draws for clinical and research purposes likely to exceed these amounts? [ ] Yes [X]No If "Yes," comment on associated risks.

D. DRUGS AND OTHER SUBSTANCES.

1. Will an Investigational new drug (IND) or other investigational substance be used in the study? [ ] Yes [X] No If "Yes," provide the following information about each drug/substance: (Add sheets if necessary.)

Name		Dosage	Route of Administration	Phase of Testing	IND#	Side Effects
Generic	Trade					

For each IND, provide one copy of the drug Protocol and of the following information:

- **toxicity data**
- **reports of animal studies**
- **reports of human studies in adults and children**

NOTE: For sponsored studies, the bulleted information is usually contained in the "Investigator's Brochure" written by the sponsor. If the study is not sponsored or if there is no "Investigator's Brochure," prepare a brief summary of this information for the Board and, if available, attach relevant articles.

2. Has the distribution process been reviewed with the hospital Investigational Drug Service?
[ ] Yes [ ] No, explain

3. Will other drugs or substances be used? [X] Yes [ ] No If "Yes," provide the following information about each drug/substance: (Add sheets if necessary.)

Name		Dosage	Route of Administration	Side Effects
Generic	Trade			
glucose 25%	various	0.5k9 body wt.	intravenous catheter	
		(max of 35)		

For each drug specify:

a. Has the drug/substance been labeled for use with children in the proposed age group? [X] Yes[ ] No

b. Has the drug/substance been labeled for this use? [X] Yes [ ] No

c. Has the drug/substance been approved in this form? [X] Yes [ ] No

NOTE: If the answer to a., b., or c. Is "No," the drug or substance you wish to study may be considered investigational, requiring an IND number from the FDA. Call Research Administration (526-2139 or 526-2023) for more information.

E. DEVICES.

Will an investigational device be used? [ ] Yes [X] No

NOTE: If "Yes," provide name, source, description, how used, and FDA's investigational device exemption (IDE) number. If there is no IDE, explain and include a statement as to why the device qualifies as a non-significant risk device. Attach one copy of the protocol, descriptions of studies in animals and humans, and drawings or photographs of the device.

F. OTHER INFORMATION

1. **Will medical or academic records be used? (circle or indicate which) If "Yes", explain which records will be used:** Yes [X] **No**
2. **Will written consent form(s) be used?** [X] Yes [ ] No Written consent is required in most cases (in addition to an oral explanation). If "No," explain why a written consent form will not be used.

A NOTE ABOUT CONSENT FORMS:

LAY LANGUAGE The language and syntax of the consent form should be directed to the lay reader at the 6th grade level. Scientific or medical terminology should be defined within the document itself, or avoided when possible. Even those parents who use medical terms in conversation may not understand their meaning.

FORMAT. The CHRMC IRB prefers that consent forms adhere to a standard format as shown in the sample form on pages 11-13. Whether this or another format is used, the Investigator is responsible for including all necessary information as required by the federal regulations, as well as additional information required by the Board. (This information is included as a checklist in the sample form .)

SIGNATURES. Federal regulations require that consent be obtained from both parents unless: (a) the research involves no greater than minimal risk; or (b) the research involves greater than minimal risk but presents the prospect of direct benefit to the child; or (c) one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

3. **Will assent be obtained?**[X] Yes [ ] **No If "No," explain why assent will not be obtained.**

A NOTE ABOUT ASSENT FORMS

REQUIREMENT FOR ASSENT. Assent (either written or oral) is required in most cases unless: (a) the child is incapable of understanding the research Intervention; or (b) the research intervention holds out the prospect of direct benefit to the child which is available only within the context of the research. (For drug studies, this means that assent is usually required in studies that include randomization to placebo.)

WRITTEN ASSENT is required from children 7 years or older who are able to read and understand the research intervention. Children age 12 years and older may indicate assent by co-signing the consent form for their parents. A simplified written assent form is required for children age 7•11.

ORAL ASSENT is required from children younger than 7 who are old enough to understand the research Intervention.

LANGUAGE AND CONTENT. The language and syntax of the assent form must be geared to the cognitive level of the children being asked to participate. Procedures or aspects of procedures which are part of the study but not part of the child's care must be clearly described as optional. Any information that will affect the child's decision should be included, e.g., the involvement of to the child's teacher to provide behavioral information or of playmates to serve as control subjects. Samples of oral and written assent documents are included on page 14.